A STUDY ON "CORRELATION BETWEEN EPICARDIAL FAT PAD THICKNESS AND ACUTE CORONARY SYNDROME"

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Approval No. : 384

This is to certify that The Research Proposal / Project titled

CORRELATION BETWEEN EPICARDIAL FAT PAD THICKNESS AND ACUTE CORONARY SYNDROME

submitted by Dr. P.K. DEEPTHI **of**

Dept. of GENERAL MEDICINE **Thanjavur Medical College, Thanjavur**

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This is to certify that this dissertation entitled "**A STUDY ON CORRELATION BETWEEN EPICARDIAL FAT PAD THICKNESS AND ACUTE CORONARY SYNDROME"** is the bonafide record work done by Dr.P.K.DEEPTHI, submitted as partial fulfilment for the requirements of M.D. Degree Examinations, General Medicine (Branch I) to be held in May 2018.

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I solemnly declare that the dissertation titled **"A STUDY ON CORRELATION BETWEEN EPICARDIAL FAT PAD THICKNESS AND ACUTE CORONARY SYNDROME"** was done by me from MARCH 2017 to AUGUST 2017 under the guidance and supervision of **PROF. DR. C.BABU ANAND M.D.**

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CERTIFICATE – II

This is to certify that this dissertation word ***"A STUDY ON CORRELATION BETWEEN EPICARDIAL FAT PAD THICKNESS AND ACUTE CORONARY SYNDROME"*** of the candidate DR.P.K.DEEPTHI with registration Number 201511202 for the award of M.D in the branch of General Medicine. I personally verified the urkund.com website for the purpose of plagiarism Check. I found that the uploaded thesis file contains from introduction to conclusion pages and result shows 3 (percentage) of plagiarism in the dissertation.

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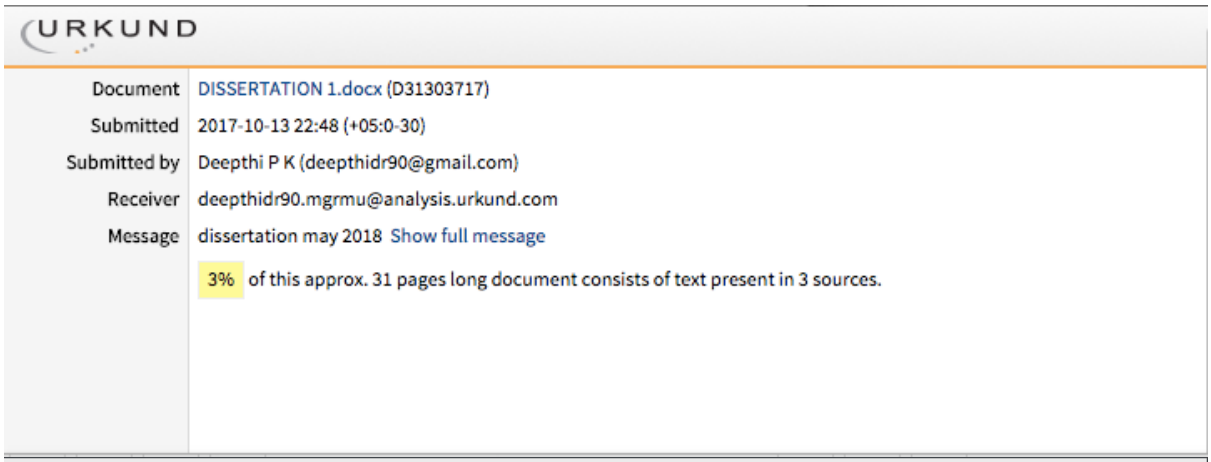

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Instances where selected sources appear:

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LIST OF ABBREVIATIONS USED

ABC – ATP BINDING CASSETTE

ABI – ANKLE BRACHIAL INDEX

ACC/AHA – AMERICAN COLLEGE OF CARDIOLOGY/AMERICAN HEART ASSOCIATION.

ACE – ANGIOTENSIN CONVERTING ENZYME

ADIPOQ – ADIPONECTIN

AF – ATRIAL FIBRILLATION

AMP – ADENOSINE MONOPHOSPHATE

APO B – APOLIPOPROTEIN B

APO CIII – APOLIPOPROTEIN CIII

ASCVD – ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

ATP – ADENOSINE TRIPHOSPHATE

BH_4 - TETRAHYDROBIOPTERIN

BMI – BODY MASS INDEX

BP – BLOOD PRESSURE

CABG – CORONARY ARTERY BYPASS GRAFT

CAC – CORONARY ARTERY CALCIUM

CAD – CORONARY ARTERY DISEASE

CD – CLUSTER OF DIFFERENCIATION

CIMT – CAROTID INTIMA MEDIA THICKNESS

CRP – C-REACTIVE PROTEIN

CV – CARDIO VASCULAR

CVD – CARDIOVASCULAR DISEASE

DASH – DIETARY APPROACH TO STOP HYPERTENSION

DM – DIABETES MELLITUS

EAT – EPICARDIAL ADIPOSE TISSUE

EF – EPICARDIAL FAT

eNOS – ENDOTHELIAL NITRIC OXIDE SYNTHETASE

HDL – HIGH DENSITY LIPOPROTEIN

IFN – INTERFERON

IHD – ISCHAEMIC HEART DISEASE

iNOS – INDUCIBLE NITRIC OXIDE SYNTHETASE

KLF 2 – KRUPPEL LIKE FACTOR 2

LDL – LOW DENSITY LIPOPROTEIN

MCP 1 – MONOCYTE CHEMOATTRACTANT PROTEIN

MI – MYOCARDIAL INFARCTION

MS – METABOLIC SYNDROME

mTOR – MECHANISTIC TARGET OF RAPAMYCIN

NADPH – NICOTINAMIDE ADENINE DINUCLEOTIDE PHOSPHATE

NCEP-ATP III – NATIONAL CHOLESTEROL EDUCATION PROGRAM-ADULT TREATMENT PANEL III

OSA – OBSTRUCTIVE SLEEP APNOEA

PCI – PERCUTANEOUS CORONARY INTERVENTION

PCOS – POLYCYSTIC OVARIAN SYNDROME

PDGF – PLATELET DERIVED GROWTH FACTOR

PVAT – PERIVASCULAR ADIPOSE TISSUE

RNA – RIBONUCLEIC ACID

ROS – REACTIVE OXYGEN SPECIES

SD – STANDARD DEVIATION

TGF B – TRANSFORMING GROWTH FACTOR BETA

TNF – TUMOR NECROSIS FACTOR

TZD – THIAZOLIDINEDIONES

VAT – VISCERAL ADIPOSE TISSUE

VLDL – VERY LOW DENSITY LIPOPROTEIN

WC – WAIST CIRCUMFERENCE

CONTENTS

INTRODUCTION

Atherosclerosis remains the major cause of death and premature disability all over the world. Current prediction estimate that by the year 2020, the leading global cause of total disease burden will be the cardiovascular diseases particularly atherosclerosis[69].

The metabolic syndrome consist of a group of metabolic abnormalities that leads to increased risk of cardiovascular disease and diabetes mellitus. The major features of metabolic syndrome are central obesity, hypertriglyceridemia, decreased high density lipoprotein level, hyperglycemia and hypertension[67].

Cardiovascular risk of obesity is more strongly associated with visceral adiposity and not with subcutaneous adiposity is well established now. For visceral obesity, anthropometric variables such as body mass index (BMI) and waist circumference (WC) have only limited sensitivity and specificity. “Normal weight obese “ persons are those who are having normal WC but with increased visceral obesity. They are prone to same risk of metabolic syndrome as obese persons[12].

Non-invasive cardiac imaging techniques like transthoracic echocardiogram can be used to quantify VAT (visceral adipose tissue). It has been validated as an easy and reliable method . It is done by measuring the EAT (Epicardial adipose tissue) . EAT correlates well with the presence of general VAT. Epicardial adipose tissue is becoming more sensitive and specific indicators of cardiometabolic risk. These fat depots has independent risk for cardiovascular disease[61].

In this study the relationship between epicardial fat pad thickness and incidence of myocardial infarction is evaluated.

OBJECTIVES

- To evaluate the correlation between epicardial fat pad thickness measured by echocardiography and incidence of acute coronary syndrome.

REVIEW OF LITERATURE

GLOBAL TRENDS OF ISCHAEMIC HEART DISEASE :

IHD (Ischaemic Heart Disease) causes more death and disability in the world. It incurs more economic costs than others illness in the world. It is the most common , serious, chronic, life threatening illness in the world. Around 13 million persons have IHD in the world. Out of them >6 million have angina pectoris and >7 million have sustained a myocardial infarction[62].

Emergence of IHD are associated with genetic factors, high fat diet and energy rich diet, smoking and a sedentary lifestyle. Now it became more prevalent in low socio-economic groups[62].

Obesity , insulin resistance, and type 2 diabetes mellitus are increasing. Now they are becoming the powerful risk factors for IHD. Emerging economics leads to, urbanization in countries. Therefore elements of energy rich western diet are being adopted in those countries. This leads to rapid increase in both the risk factors for IHD and IHD . There is a shift from communicable to non-communicable diseases. The most common cause of death worldwide by 2020 is IHD probably[62].

METABOLIC SYNDROME

Metabolic syndrome includes several cardiometabolic risk factors. They are characterized by four essential components which includes intra-abdominal obesity, dyslipidemia, hypertension and impaired glucose tolerance[63,64]. It is linked to a high risk of both type 2 diabetes and CAD. It increased the risk of cardiovascular events[63,65,66].

Intra-abdominal circumference (Visceral adipose tissue) is considered most strongly related to insulin resistance. It also has the risk of diabetes and CVD. The distribution of adipose tissue between subcutaneous tissue and visceral depots vary substantially for any given waist circumference. Thus for any two persons with same waist circumference the risk may vary[67].

The prevalence of metabolic syndrome increases with age. Nearly 60% of women of age group 45-49 and 45% of men of age group 45-49 are suffering from metabolic syndrome. Women were found to have higher values for waist circumference. High plasma triglyceride levels (> 150 mg/dl) ,low HDL level and high blood sugar values were more common in men[67].

RISK FACTORS

OVERWEIGHT/OBESITY :

Central obesity is the most important defining feature of metabolic syndrome. There is a positive correlation between waist circumference and increasing adipose tissue. Normal weight doesn't exclude the chances for a patient to have insulin resistance or increased adipose tissue.

SEDENTARY LIFESTYLE :

Sedentary life style is well known to have an increased association with high cardiovascular mortality and morbidity. Increased central adiposity, low levels of HDL, hypertriglyceridemia , hypertension and glucose intolerance is found to be associated with metabolic syndrome [67]. This relationship was identified more with genetic predisposition.

AGING :

Fifty percentage of persons older than age 50 are affected. Women greater than 60 years are often affected by metabolic syndrome than men[67].

DIABETES MELLITUS:

Impaired glucose tolerance or Diabetes is a major risk factor for metabolic syndrome.

ETIOLOGY

INSULIN RESISTANCE :

Insulin resistance is considered as the key pathogenesis in metabolic syndrome. The onset of insulin resistance is marked chronologically by

- Postprandial hyper insulinemia
- Fasting hyperinsulinemia
- Hyperglycemia [67].

Triglycerides which are stored in adipose tissue contains free fatty acids which are plasma bound. These stores are released by intracellular lipolytic enzymes. Lipoprotein lipase causes lipolysis of triglyceride rich lipoproteins in tissues. Insulin mediates anti lipolysis. It also causes stimulation of lipoprotein lipase in adipose tissue. The most sensitive action of insulin is the inhibition of lipolysis. When insulin resistance develops increased lipolysis produces more fatty acids. It further decreases the anti-lipolytic effect of insulin. The uptake of glucose which is mediated by insulin is reduced by fatty acids. These glucose are stored as triglycerides in cardiac and skeletal muscles in excess. Excess glucose are produced and it gets accumulated in the liver. The excess triglycerides are also stored in liver[67].

Leptin has effects on energy hemostasis, neuroendocrine, immunity and reproductive function. Leptin resistance can also lead to metabolic syndrome. When obesity develops, hyperleptinemia ensues with leptin resistance. It leads

to inflammation, insulin resistance, hyperlipidaemia, CVD, atherosclerosis and heart failure[67].

INCREASED WAIST CIRCUMFERENCE :

Waist circumference is included as essential criteria for this syndrome diagnosis. But waist circumference does not distinguish between visceral adipose tissue from subcutaneous fat. Increase in visceral adipose tissue occurs in metabolic syndrome. Free fatty acids which are produced from adipose tissue gets stored in the liver. There is increased prevalence of the metabolic syndrome in those with relative increase in visceral versus subcutaneous adipose tissue. The marker for excess postprandial free fatty acids in obesity is visceral fat[67].

DYSLIPIDEMIA :

An excellent marker of insulin resistant condition is hypertriglyceridemia. Patient with metabolic syndrome have elevated level of Apo CIII. All lipoproteins carry Apo CIII. When this level gets elevated it increases triglyceride level. It is also associated with more atherosclerotic cardiovascular disease[67].

Reduction in HDL cholesterol is the other major lipoprotein disturbance occurring in metabolic syndrome. It is due to the change in HDL composition and the mechanism of its clearance. Due to this change , HDL gets metabolised very quickly. This mechanism can lead to insulin resistance[67].

In metabolic syndrome , low-density lipoproteins (LDLs) are also modified in composition. Predominance of small dense LDLs occurs with fasting serum triglycerides of > 180 mg/dl. They are thought to be more atherogenic. But their independent association with CVD events is not known. Patients having elevated triglyceride level have elevated levels of VLDL1 and VLDL2.The particle number of LDL particles is also high in those patients. The above changes can lead to atherosclerosis in high risk patients[67].

GLUCOSE INTOLERANCE :

The action of insulin is reduced in this syndrome. So the production of glucose by kidney and liver is reduced. In tissues highly sensitive to insulin like muscle and adipose tissue, the uptake of glucose is reduced. There is relationship between impaired glucose tolerance and insulin resistance. It is well supported by various studies. Compensation for defect in insulin action is needed. So maintain normal glucose level, the secretion of insulin and its metabolism should be changed. Usually there is defect in insulin secretion. So this compensatory mechanism fails. This leads to elevated fasting blood sugar level and finally patient develops diabetes mellitus[67].

HYPERTENSION :

Hypertension is also one of the important cause of this syndrome. Insulin has an important function in the kidney where it dilates the renal blood vessels. It also causes sodium reabsorption from the tubules under normal

physiological conditions. But when insulin resistance develops, this major effect of dilating the renal arteries is lost. The function of reabsorption of sodium is present. Insulin also increases the activity of sympathetic nervous system. This action is preserved in this syndrome. The enzyme phosphatidylinositol-3-kinase signalling is reduced due to insulin resistance. It causes imbalance between production of nitric oxide and secretion of endothelin 1 in the endothelium leading to decrease in blood flow[67].

Hypertension may also be due to vasoactive role of perivascular adipose tissue . Free radicals are released from NADPH oxidase thereby affecting the endothelial function causing local vasoconstriction. Paracrine effects are mediated by the leptins and TNF . These are released from adipose tissue [67].

Another consequence of insulin resistance is hyperuricemia which commonly occurs in metabolic syndrome. Uric acid is associated with hypertension . Reduction in uric acid normalises blood pressure in adolescents with hyperuricemia and hypertension. Uric acid can stimulate renin-angiotensin-aldosterone system and may result in hypertension[67].

PROINFLAMMATORY CYTOKINES :

The adipose tissue derived macrophages is the primary source of pro inflammatory cytokines[67] such as interleukins 1, 6 and 18, resistin, tumour necrosis factor alfa and C reactive protein in the local and in systemic circulation It reflects overproduction by the expanded adipose tissue mass

ADIPONECTIN :

Adiponectin is an anti-inflammatory cytokines synthesized by adipocytes. It improves insulin sensitivity . Adiponectin prevents the expression of gluconeogenic enzymes and hence the glucose production in the liver.

In muscle adiponectin enhances glucose transport and improves the fatty acid oxidation through activation of AMP kinase. Adiponectin levels are decreased in metabolic syndrome[67].

CLINICAL FEATURES

SYMPTOMS AND SIGNS :

Symptoms typically do not occur in metabolic syndrome.

On examination one can find[67]

- Increased waist circumference
- Elevated blood pressure
- Lipoatrophy
- Acanthosis nigricans

ASSOCIATED DISEASES

CARDIOVASCULAR DISEASE :

In patients without any previous history of diabetes mellitus with metabolic syndrome has 1.5 to 3.5 times higher CVD risk.. Patients with metabolic syndrome are at increased risk for peripheral vascular disease[67].

TYPE 2 DIABETES MELLITUS :

There is 3 to 5 fold increase in the risk for type 2 diabetes mellitus in patients with metabolic syndrome[67].

Other features include increase in ApoB and ApoCIII, uric acid, prothrombin factors like fibrinogen, platelet activator inhibitor 1,increase in serum viscosity, asymmetric dimethylarginine, homocysteine, white blood cell count, proinflammatory cytokines, C-reactive protein, macroalbuminuria,

The other conditions associated include non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, polycystic ovary syndrome and obstructive sleep apnoea[67].

NASH, a common emerging cause for both cirrhosis liver & hepatocellular carcinoma is increasing in the world population as the incidence of obesity ascends.

HYPERURICEMIA :

Hyperuricemia shows impaired insulin action on the renal tubular reabsorption of uric acid which can cause endothelial dysfunction and hypertension.

POLYCYSTIC OVARIAN SYNDROME (PCOS) :

Polycystic ovarian disease and metabolic syndrome are two sides of a coin which has strong association with insulin resistance there is a threefold increased risk of developing metabolic syndrome in women with PCOS than those without syndrome[67].

OBSTRUCTIVE SLEEP APNOEA (OSA) :

Obstructive sleep apnoea is associated with obesity, hypertension, increased circulatory cytokines, impaired glucose tolerance and insulin resistance. On comparing the biomarkers of insulin resistance between patients with OSA with weight based controls, insulin resistance is found to be more severe with OSA. is found to increase Insulin sensitivity is increased with continuous positive airway pressure treatment in patients with OSA[67].

DIAGNOSTIC CRITERIA

NCEP:ATPIII 2001[68]

Three or more of the following :

- Central obesity : waist circumference > 102 cm(M) , > 88 cm (F)
- Hypertriglyceridemia : triglyceride level > 150 mg/dl or specific medication
- Low HDL cholesterol : < 40 mg/dl (M) , < 50 mg/dl (F)
- Hypertension: blood pressure > 130 mm Hg systolic or > 85 mm Hg diastolic or specific medication.
- Fasting plasma glucose level > 100 mg/dl or specific medication or previously diagnosed type 2 diabetes.

LABORATORY TESTS :

- Fasting lipid profile.
- Blood glucose
- High sensitive C-reactive protein
- Serum Fibrinogen
- Serum Uric acid
- Urinary microalbumin
- Liver function test
- Sleep study if there is symptoms of OSA

- Follicle stimulating hormone, luteinizing hormone, testosterone if PCOS is suspected[67].

TREATMENT

LIFESTYLE MODIFICATIONS :

Weight reduction is the primary approach to this disorder since obesity is the driving force behind metabolic syndrome. In general recommendations for weight loss include a combination of

- Reduction in calorie intake
- Increased exercise
- Behaviour modification.

Some evidence suggest that addition of exercise to caloric restriction may promote greater weight loss from the visceral depots. The tendency for weight regain after successful weight reduction is common. So it underscores the need for long lasting behaviour changes[67].

DIET :

It may have taken a long time to develop expanded fat mass for the patient. So correction need not occur quickly. Diet restricted in carbohydrates typically provides rapid initial weight loss. High quality diet rich in fruits, vegetables, whole grains, lean poultry and fish should be encouraged to maximise overall health benefit[67].

PHYSICAL ACTIVITY :

It is important to ensure that increased activity does not incur risk in patients with metabolic syndrome. Before initiating the exercise program, some high risk patient should undergo formal cardiovascular evaluation. For inactive participant gradual increase in physical activity should be encouraged. This is to enhance adherence and to avoid injury. 60-90 min of physical activity is required to achieve the goal. In obese individuals atleast half an hour of moderate intensity physical activity like gardening, walking, house cleaning is advocated[67]

BEHAVIOUR MODIFICATION :

Behaviour treatment typically includes recommendation for dietary restriction and more physical activity which results in weight loss. Duration of the program should be designed in such a way that it wont cause a weight regain after successful weight reduction. Patients can be provided information through TV, internet, etc. It is to maintain contact with the providers and the patients[67].

OBESITY :

Treatment options need to extend beyond life style modification in some patients. Weight loss drugs comes in two major groups :

- Appetite suppressants
- Absorption inhibitors

Appetite suppressants :

- Phentermine/topiramate combination
- Lorcaserin.

Side effects :

Phentermine / topiramate : palpitations, headache, paresthesias, constipation , insomnia

Lorcaserin : headache, nasopharyngitis.

Absorption inhibitor - Orlistat

- Inhibits fat absorption.
- Reduces the incidence of type 2 diabetes.
- Side effect : oily leakage per rectum.

Metabolic or Bariatric surgery :

Indications :

- Patients with BMI > 40 kg/m2 0r >35 kg/m2 with co-morbidities.
- Diabetic patients with BMI around 30 kg/m2.

Procedure :

Gastric bypass or sleeve gastrectomy which causes drastic weight reduction and improvement in features of metabolic syndrome. A survival benefit with this surgery has also been realised[67].

LDL CHOLESTEROL

Statins should be prescribed for the patients with metabolic syndrome with diabetes mellitus. The current evidence support a maximum of penultimate dose of potent statins. It has benefits for the patients with diabetes and CVD. Statins should be given for a patient with metabolic syndrome having a score (that predicts 10 year CVD risk) exceeding 7.5% . If the 10 year risk of developing CVD is <7.5% statin use is not recommended[67].

Diet restricted with saturated fat (< 7% of calories) and trans-fats should be strictly applied. Dietary cholesterol should also be restricted. Pharmacological intervention is needed if LDL cholesterol remains elevated despite dietary restrictions. Statins reduces LDL cholesterol by 15-60%. Hepatotoxicity is rare and myopathy is seen in 10% of patients taking statins[67].

The second choice of medication intervention is ezetimibe which is the cholesterol absorption inhibitor. Ezetimide reduces LDL cholesterol by 15-20%[67].

The bile acid sequestrants are

- Cholestyramine
- Colestipol
- Colesevalam

These are more effective than ezetimibe but they increase triglyceride levels. So it should be used with caution in patients with metabolic syndrome. It should not be administered if the fasting triglyceride level is > 250 mg/dl.

Gastrointestinal symptoms like belching, bloating, palatability, constipation and anal irritation are the side effects[67].

Nicotinic acid is not used to reduce LDL level. Fibrates can be administrated if both LDL and triglyceride are elevated. Fenofibrate may be more effective than gemfibrozil[67].

TRIGLYCERIDES :

A fasting triglyceride level < 150 mg/dl is required for patients with metabolic syndrome. Obesity is the main cause so patients should reduce the weight [67]. It is also necessary to reduce triglyceride level.

Fibrates lowers fasting triglyceride levels. They typically reduces triglyceride level by 30-45%. Concomitant administration of statins increase the risk of myopathy[67].

Other drugs that lower triglyceride levels include statins, nicotinic acid, and in high doses – omega -3 fatty acids. So intermediate or more statins is required. Omega-3 fatty acids preparations like docosahexaenoic acid plus eicosapentanoic acid or eicosapentanoic acid alone lower fasting triglyceride level by 30-40%. No drug reaction occurs with other drugs. The main side effect of this drug is eructation with a fishy taste. The taste can be partially blocked by ingestion of the nutraceutical after freezing[67].

HDL CHOLESTEROL :

Only few lipid modifying compounds increase HDL level. Nicotinic acid is the only currently available drug. It has predictable HDL cholesterol raising properties. It has dose related response. It increases HDL cholesterol by 30% above baseline. There is no evidence till now that raising HDL with nicotinic acid beneficially affects CVD patients with or without metabolic syndrome[67].

BLOOD PRESSURE :

The direct relationship between blood pressure and mortality rate has been well established in metabolic syndrome.

- ACE inhibitor
- Angiotensin II receptor blocker

are beneficial to decrease the occurrence of new onset type 2 diabetes. These are the initial choice of antihypertensive medication in patients who have metabolic syndrome without diabetes. A sodium restricted dietary pattern that are enriched with fruits and vegetables, whole grains, and low fat diary product should be advocated. Self-monitoring of blood pressure helps in good blood pressure control[67].

IMPAIRED FASTING GLUCOSE :

Correction of glucose intolerance in diabetes can result in improvement of the fasting lipid profile. In patients who have increased blood sugar level and not a diabetic , a lifestyle intervention including

- Reducing BMI
- Restriction of fatty food intake
- Increased exercise

can reduce the incidence of type 2 diabetes. Metformin also reduces the incidence of diabetes but the effect is less pronounced than lifestyle intervention[67].

INSULIN RESISTANCE :

Biguanides and thiazolidinediones (TZDs) increases sensitivity of insulin. Insulin resistance is the major pathological mechanism in metabolic syndrome. So the representative drugs in these classes reduce its prevalence[67].

Both the classes of drugs enhance the insulin action in the liver. They also reduces production of glucose in the body. TZDs also helps in increasing the glucose uptake in tissue such as muscle and adipose tissue[67]. These drugs have great use in have been seen in patients with non-alcoholic fatty liver disease and polycystic ovarian syndrome. The drugs have been shown to reduce the markers of inflammation[67].

PATHOGENESIS OF ATHEROSCLEROSIS

There are many generalized or systemic risk factors predispose to the development of atherosclerosis. It affects only preferentially in various regions of the circulation .It has distinct clinical manifestations that depend on the particular circulatory bed affected. Atherosclerosis of the coronary arteries commonly causes myocardial infarction and angina pectoris[69].

Within a particular arterial bed, stenoses due to atherosclerosis tend to occur. It typically in certain predisposed regions. In the coronary circulation it is the proximal left anterior descending coronary artery. It has the particular predilection for developing atherosclerotic disease[69].

The various manifestations of atherosclerosis is not only due to the stenotic, occlusive disease. It is also due to ectasia and the development of aneurysmal disease, which occur frequently in the aorta. Non occlusive intimal atherosclerosis also occurs diffusely in affected arteries in addition to focal, flow-limiting stenoses [69].

Formation of atherosclerotic plaques takes many decades. Growth of atherosclerotic plaques probably occur discontinuously. It remains silent for many years then suddenly there may be fast progression [69].

Atherosclerosis is a slow progressive process. It may present as stable angina pectoris or intermittent claudication. An acute clinical event can also occur as mentioned above[69].

INITIATION OF ATHEROSCLEROSIS :

Studies shows that the “fatty streak” is the first sign of atherosclerosis.which arises from the lipoproteins in the intima. Atherosclerosis is causally related to the fraction of lipoproteins. They are low-density lipoprotein (LDL) that bear apolipoprotein B. This is not because of increased permeability or due to “leakiness,” of the overlying endothelium . The mechanism is that the lipoproteins may collect in the intima of arteries[69]. In the wall of the artery they bind to the matrix and the resident time of lipids are prolonged.

Lipoproteins are stored in excess in the extracellular space of the intima of arteries. They often has the association with proteoglycans of the arterial extracellular matrix. This interaction may slow the egress of these lipid-rich particles from the intima. Lipoprotein particles is present in the extracellular space of the intima. They are retained by binding to matrix macromolecules. They may undergo oxidative modifications[69].

There is a pathogenic role for products of oxidized lipoproteins in atherogenesis. From the extracellular matrix, the lipoproteins are released .It give rise to breakdown products of fatty acids and phospholipids. Apoprotein moieties are changed by various molecular mechanisms.[69]

There is local production of hypochlorous acid by myeloperoxidase associated with inflammatory cells. It occurs within the plaque. It yields chlorinated species such as chlorotyrosyl moieties[69].

LEUKOCYTE RECRUITMENT :

The formation of early atherosclerotic lesions is characterized by accumulation of leukocytes . Thus, atherogenesis involves elements of inflammation. It is a process that now provides a unifying theme in the pathogenesis of this disease[69].

The cells present in the lesion are

- Monocyte-derived macrophages
- Dendritic cells
- T and B lymphocytes
- Mast cells.

Hypercholesterolemia augments the portion of particularly proinflammatory monocytes in blood. It preferentially enter the nascent atheroma . A number of adhesion molecules or receptors for leukocytes expressed on the surface of the arterial endothelial cell. It probably participate in the recruitment of leukocytes to the nascent atheroma. Proinflammatory cytokines can augment the expression of leukocyte adhesion molecules[69].

Laminar shear forces are encountered in most regions of normal arteries. It also can suppress the expression of leukocyte adhesion molecules. Atherosclerotic lesions predilection sites often have low shear stress and/or disturbed flow. Normally there is ordered, pulsatile laminar shear of normal blood flow. It augments the production of nitric oxide by endothelial cells. This molecule has vasodilator properties. It can also act at the low levels which is constitutively produced by arterial endothelium as a local anti-inflammatory autacoid, e.g., limiting local adhesion molecule expression[69].

Exposure of endothelial cells to laminar shear stress increases the transcription of Krüppel-like factor 2 (KLF2). It augments the activity of numerous salutary endothelial functions including nitric oxide synthase[69].

Laminar shear stress also stimulates endothelial cells to produce superoxide dismutase which is an antioxidant enzyme.. It potentially explain the favoured localization of atherosclerotic lesions. Those are the sites that experience disturbed flow or low shear stress[69].

They are captured on the surface of the arterial endothelial cell by adhesion receptors. Then the leukocytes penetrate the endothelial layer and take up residence in the intima. In addition to products of modified lipoproteins, cytokines (protein mediators of inflammation) such as interleukin 1 (IL-1) and tumor necrosis factor (TNF) can regulate the expression of adhesion molecules. These molecules are involved in leukocyte

recruitment which expresses the leucocyte adhesion molecules int the intima causing cytokine release. This pathway may provide an additional link between arterial accumulation of lipoproteins and leukocyte recruitment. Chemoattractant cytokines appear to direct the migration of leukocytes into the arterial wall[69].

FOAM CELL FORMATION :

Within the intima, the mononuclear phagocytes mature into macrophages and become lipid-laden foam cells.mediated by receptor mediated endocytosis. The exogenous cholesterol suppresses expression of the LDL receptor. Thus, under conditions of cholesterol excess, the level of this cell-surface receptor for LDL decreases [69].

There are candidates for alternative receptors. They can mediate lipid loading of foam cells. It include a number of macrophage "scavenger" receptors, which preferentially endocytose modified lipoproteins. It also include receptors for oxidized LDL or very low-density lipoprotein (VLDL)[69].

- Monocyte attachment to the endothelium
- Migration into the intima, and
- Maturation to form lipid-laden macrophages

represent key steps in the formation of the fatty streak. It is the precursor of fully formed atherosclerotic plaques[69].

ATHEROMA EVOLUTION AND COMPLICATIONS :

The fatty streak usually precedes the development of a more advanced atherosclerotic plaque. Not all fatty streaks progress to form complex atheromata. The mononuclear phagocytes bearing such scavenger receptors ingest the lipids from the extracellular space. They may remove lipoproteins from the developing lesion[69].

Some lipid-laden macrophages may exports lipid when leaving the artery wall. The amount of lipid entering the artery wall can exceeds than which is removed by mononuclear phagocytes or other pathways. This leads to lipid accumulation. Hence it has the propensity to form an atheroma. Macrophages also proliferate in plaques . It occurs in response to hematopoietic growth factors overexpressed in lesions. It is another aspect of the dynamic regulation and flux of cells during atherogenesis[69].

Export by phagocytes may constitute one response to local lipid overload in the evolving lesion[69].

There is another mechanism .It is reverse cholesterol transport mediated by high-density lipoproteins (HDLs). It probably provides an independent pathway for lipid removal from atheroma. This transfer of cholesterol from the cell to the HDL particle involves specialized cell-surface molecules .These molecules are the ATP binding cassette (ABC) transporters. “Reverse cholesterol transport” is mediated by these ABC transporters. It allows HDL

loaded with cholesterol to deliver it to hepatocytes by binding to scavenger receptor B1 or other receptors[69].

The liver cell can metabolize the sterol to bile acids .It can be excreted. Thus, during atherogenesis, macrophages may play a vital role in the dynamic economy of lipid accumulation in the arterial wall [69].

There are some lipid-laden foam cells within the expanding intimal lesion that usually perish. Some foam cells may die due to programmed cell death, or apoptosis. This death of mononuclear phagocytes results in the formation of the lipid-rich center. It is called the necrotic core, in established atherosclerotic plaques. There may be impaired clearance of dead foam cells (efferocytosis) in plaques. It may hasten lipid core formation[69].

Macrophages loaded with modified lipoproteins may elaborate microparticles or exosomes (which may contain regulatory microRNAs), cytokines, and growth factors. They can further signal some of the cellular events in lesion complication. Accumulation of lipid laden macrophages characterizes the fatty streak[69].

The smooth-muscle cell synthesizes the bulk of the extracellular matrix. It is the matrix of the complex atherosclerotic lesion. There are a number of growth factors or cytokines elaborated by mononuclear phagocytes. They can stimulate smooth-muscle cell proliferation and production of extracellular matrix. Cytokines found in the plaque are IL-1 and TNF. It can induce local

production of growth factors, including forms of platelet-derived growth factor (PDGF), fibroblast growth factors, and others. They may contribute to plaque evolution and complication[69].

Other cytokines, notably interferon gamma (IFN-gamma) are derived from activated T cells within lesions. They can limit the synthesis of interstitial forms of collagen by smooth-muscle cells[69].

The accumulation of smooth-muscle cells and their elaboration of extracellular matrix provide a critical transition. They yield a fibrofatty lesion in place of a simple accumulation of macrophage derived foam cells[69].

PDGF is elaborated by activated platelets, macrophages, and endothelial cells. It can stimulate the migration of smooth-muscle cells that are normally resident in the tunica media into the intima. These growth factors and cytokines are produced locally. They can stimulate the proliferation of resident smooth-muscle cells or resident stem cells in the intima and also that may migrate in from the media[69].

Transforming growth factor beta (TGF-beta), potently stimulates interstitial collagen production by smooth muscle cells. These mediators may arise from neighbouring vascular cells or leukocytes (a “paracrine” pathway). They also arises from the same cell that responds to the factor (an “autocrine” pathway)[69].

These alterations in smooth-muscle cells are signalled by these mediators acting at short distances. It can hasten transformation of the fatty streak into a more fibrous smooth-muscle cell and extracellular matrix—rich lesion[69].

. Fatty streak formation usually begins beneath a morphologically intact endothelium. In advanced fatty streaks, microscopic breaches in endothelial integrity may occur[69].

Microthrombi rich in platelets can form at such sites of limited endothelial denudation. It forms owing to exposure of the thrombogenic extracellular matrix of the underlying basement membrane. Activated platelets release numerous factors that can promote the fibrotic response. These include PDGF and TGF-beta. Thrombin generates fibrin during coagulation. It also stimulates protease-activated receptors. These receptors can signal smooth muscle migration, proliferation, and extracellular matrix production[69].

Many arterial mural microthrombi resolve without clinical manifestation by spontaneous lysis and resorption. It can lead to lesion progression by stimulating these profibrotic functions of smooth-muscle cells[69].

MICROVESSELS FORMATION :

Newly developing microvascular networks are there which may contribute to lesion complications in several ways. These blood vessels provide an abundant surface area for leukocyte trafficking . They may serve as the portal for entry and exit of white blood cells from the established atheroma[69].

Microvessels in the plaques may also furnish foci for intraplaque hemorrhage. Microvessels in the atheroma may be friable. So they are prone to rupture and can produce focal haemorrhage, like the neovessels in the diabetic retina . Such a vascular leak can provoke thrombosis in situ. Thus yielding local thrombin generation. This in turn can activate smooth-muscle and endothelial cells through ligation of protease activated receptors[69].

Atherosclerotic plaques often contain fibrin and hemosiderin. It is an indication that episodes of intraplaque haemorrhage contribute to plaque complications[69].

CALCIFICATION :

As they advance, calcium also gets accumulated in atherosclerotic plaques. Microvesicles derived from lesional cells can stimulate calcification. This process co-localizes with regions of heightened inflammation. Mineralization of plaques include the regulatory participation of transcription factors such as Runx2[69].

PLAQUE EVOLUTION :

Smooth-muscle cells and macrophages die in the atherosclerotic plaque. The complex atheromata often have a mostly fibrous character. They lack the cellularity of less advanced lesions. There is relative paucity of smooth-muscle cells in advanced atheromata. It may result from the predominance of cytostatic mediators such as TGF-beta and IFN-gamma (which can inhibit smooth-muscle cell proliferation) and also from smooth-muscle cell apoptosis[69].

A highly regulated balance occurring between entry and egress of lipoproteins and leukocytes, cell proliferation and cell death, extracellular matrix production, and remodelling, as well as calcification and neovascularization that finally contribute to lesion formation[69].

There are many mediators related to atherogenic risk factors. It include those derived from lipoproteins, cigarette smoking, and angiotensin II. They provoke the production of pro inflammatory cytokines causing vessel wall infiltration by the leukocytes thereby causing these lesions[69].

PATHOPHYSIOLOGICAL CONSEQUENCES OF ATHEROSCLEROSIS :

Most atheromata are asymptomatic and many usually never cause clinical manifestations. Arterial remodelling during atheroma formation occurs. It accounts for some of this variability in the clinical expression of atherosclerotic disease[69] .

The plaque usually grows outward, in an abluminal direction during the initial phases of atheroma development . Vessels affected by atherogenesis tend to increase in diameter. This phenomenon known as compensatory enlargement is a type of vascular remodeling. The growing atheroma does not encroach on the arterial lumen. It encroaches when the burden of atherosclerotic plaque exceeds 40% of the area encompassed by the internal elastic lamina. Thus, during much of its life history, an atheroma will not cause stenosis that can limit tissue perfusion[69].

Flow-limiting stenoses commonly form only later in the history of the plaque. Many such plaques cause stable syndromes. It includes demand-induced angina pectoris or intermittent claudication in the extremities. Even total vascular occlusion by an atheroma does not invariably lead to infarction in the coronary circulation and other circulations. The hypoxic stimulus due to repeated bouts of ischemia characteristically induces formation of collateral vessels in the myocardium. It mitigating the consequences of an acute occlusion of an epicardial coronary artery[69].

By contrast, many lesions can cause acute or unstable atherosclerotic syndromes, particularly in the coronary circulation. It may arise from atherosclerotic plaques that do not produce a flow-limiting stenoses. Such lesions may produce only minimal luminal irregularities on traditional angiograms. It often do not meet the traditional criteria for “significance” by arteriography. In patients who do not report prior history of angina pectoris,

the frequency of MI as an initial manifestation of coronary artery disease (CAD) may be due to thrombi arising from such non occlusive stenoses[69].

PLAQUE INSTABILITY AND RUPTURE :

A superficial erosion of the endothelium or a frank plaque rupture or fissure usually produces the thrombus. This causes episodes of unstable angina pectoris or the occlusive and relatively persistent thrombus that causes acute MI[69] .

When the rupture of the plaque's fibrous cap it permits contact between coagulation factors in the blood and highly thrombogenic tissue factor expressed by macrophage foam cells in the plaque's lipid-rich core. If the ensuing thrombus is nonocclusive or transient, the episode of plaque disruption may not cause symptoms. Sometime it may result in episodic ischemic symptoms such as rest angina[69].

Occlusive thrombi that endure often cause acute MI. It occurs particularly in the absence of a well-developed collateral circulation that supplies the affected territory. Repetitive episodes of plaque disruption and healing occur. It provide one likely mechanism of transition of the fatty streak to a more complex fibrous lesion . The healing process takes place in arteries. It involves the laying down of new extracellular matrix and fibrosis[69].

Not all atheromata exhibit the same propensity to rupture. Plaques that have caused thrombosis tend to have

- Thin fibrous caps

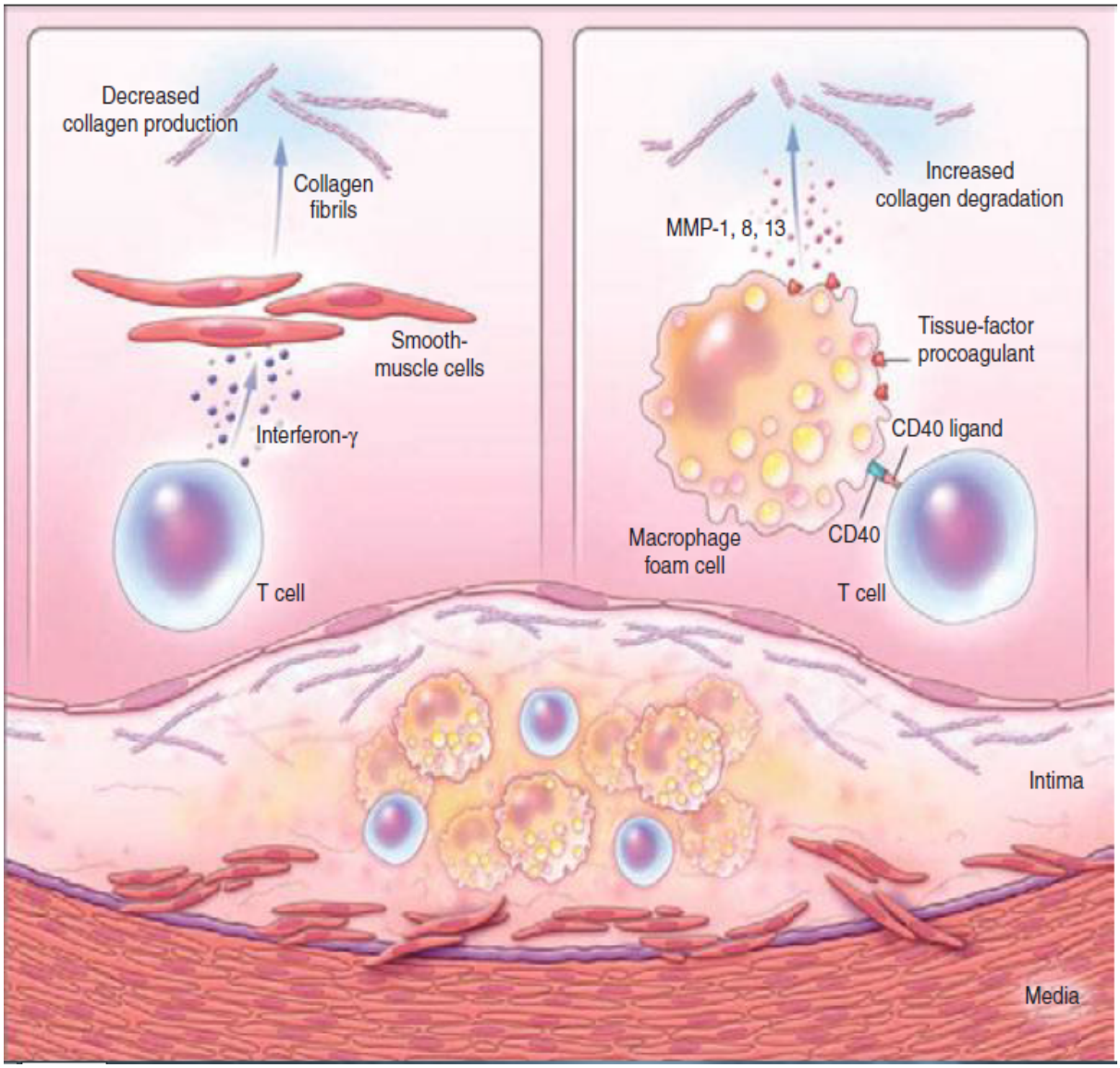
- Relatively large lipid cores
- A high content of macrophages
- Outward remodelling,
- Spotty calcification.

Morphometric studies of such culprit lesions show that at sites of plaque rupture, macrophages and T lymphocytes predominate. It contain relatively few smooth-muscle cells. The cells that concentrate at sites of plaque rupture bear markers of inflammatory activation[69].

Signs of disseminated inflammation is seen in patients with active atherosclerosis and acute coronary syndrome. Inflammatory mediators regulate processes that govern the integrity of the plaque's fibrous cap. Hence, it regulates its propensity to rupture. Cytokines derived from activated macrophages and lesional T cells can boost production of proteolytic enzymes. These enzymes can degrade the extracellular matrix of the plaque's fibrous cap[69].

Thus, inflammatory mediators can impair the collagen synthesis which is required for maintenance and repair of the fibrous cap. They trigger degradation of extracellular matrix macromolecules, processes that weaken the plaque's fibrous cap. They also enhance its susceptibility to rupture. Some plaques have a dense extracellular matrix and relatively thick fibrous cap and they do not have substantial tissue factor–rich lipid cores. They seem generally resistant to rupture and unlikely to provoke thrombosis[69].

FIGURE 1: INFLAMMATORY PATHWAYS THAT PREDISPOSE ATHEROSCLEROTIC PLAQUES TO RUPTURE AND PROVOKE THROMBOSIS[69]



RISK FACTORS FOR ATHEROSCLEROSIS :

- High LDL cholesterol
- Cigarette smoking
- Hypertension (BP ≥140/90 mmHg or on antihypertensive medication)
- Low HDL cholesterol (<1.0 mmol/L [<40 mg/dL])
- Diabetes mellitus
- Family history of premature CHD
- Age (men ≥45 years; women ≥55 years)
- Male sex and postmenopausal female[69]

Lifestyle risk factors

- Obesity (BMI ≥30 kg/m2)
- Physical inactivity
- Atherogenic diet

Emerging risk factors

- Lipoprotein (a)
- Prothrombotic factors
- Proinflammatory factors
- Impaired fasting glucose
- Subclinical atherosclerosis[69]

MANAGEMENT

LIFESTYLE MODIFICATION :

ACC/AHA 2013 Guidelines[69] :

The adult population should be encouraged to practice heart healthy

lifestyle behaviours, including:

- Consume a dietary pattern that emphasizes intake of vegetables, fruits, and whole grains; include low-fat dairy products, poultry, fish, legumes, non tropical vegetable oils, and nuts; and limit intake of sodium, sweets, sugar-sweetened beverages, and red meats.
- Adapt this dietary pattern to appropriate calorie requirements, personal and cultural food preferences, and nutrition therapy for other medical conditions (including diabetes mellitus).
- Achieve this pattern by following plans such as the DASH dietary pattern, the USDA Food Pattern, or the AHA Diet
- Engage in 2 hours and 30 minutes a week of moderate intensity or 1 hour and 15 min (75 min) a week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic physical activity. Aerobic activity should be performed in episodes of at least 10 min, preferably spread throughout the week.
- Achieve and maintain a healthy weight.

RISK ASSESSMENT :

The 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk recommends the use of newer risk markers if uncertainty persists after assessing quantitative risk using the pooled cohort calculator[69].

The guideline states that

- Family history,
- hsCRP,
- Coronary artery calcium (CAC) score, or
- Ankle-brachial index (ABI)

may then be considered to inform treatment decision making. For risk assessment for a first ASCVD event, carotid intima media thickness (CIMT) for routine measurement is discouraged in clinical practice. The guideline panel deemed the contribution to risk assessment for a first ASCVD event using the following : apolipoprotein B (ApoB), chronic kidney disease, albuminuria, or cardiorespiratory fitness as uncertain at present[69].

ISCHEMIC HEART DISEASE

Ischemic heart disease (IHD) is a condition where there is an inadequate supply of blood and oxygen to a portion of the myocardium. Imbalance between myocardial oxygen supply and demand is the commonest cause. Atherosclerotic disease of an epicardial coronary artery (or arteries) is the most common cause of myocardial ischemia. This is sufficient to cause a regional reduction in myocardial blood flow and inadequate perfusion of the myocardium supplied by the involved coronary artery[62].

PATHOPHYSIOLOGY :

There are three major determinants of myocardial oxygen demand :

- Heart rate
- Myocardial contractility
- Myocardial wall stress (tension)

Blood flows through the coronary arteries in a phasic fashion. The majority of blood flow occurs during diastole. Nearly 75% of the total coronary resistance to flow occurs across three sets of arteries:

- Large epicardial arteries (Resistance 1 = R1)
- Prearteriolar vessels (R2)
- Arteriolar and intramyocardial capillary vessels (R3).

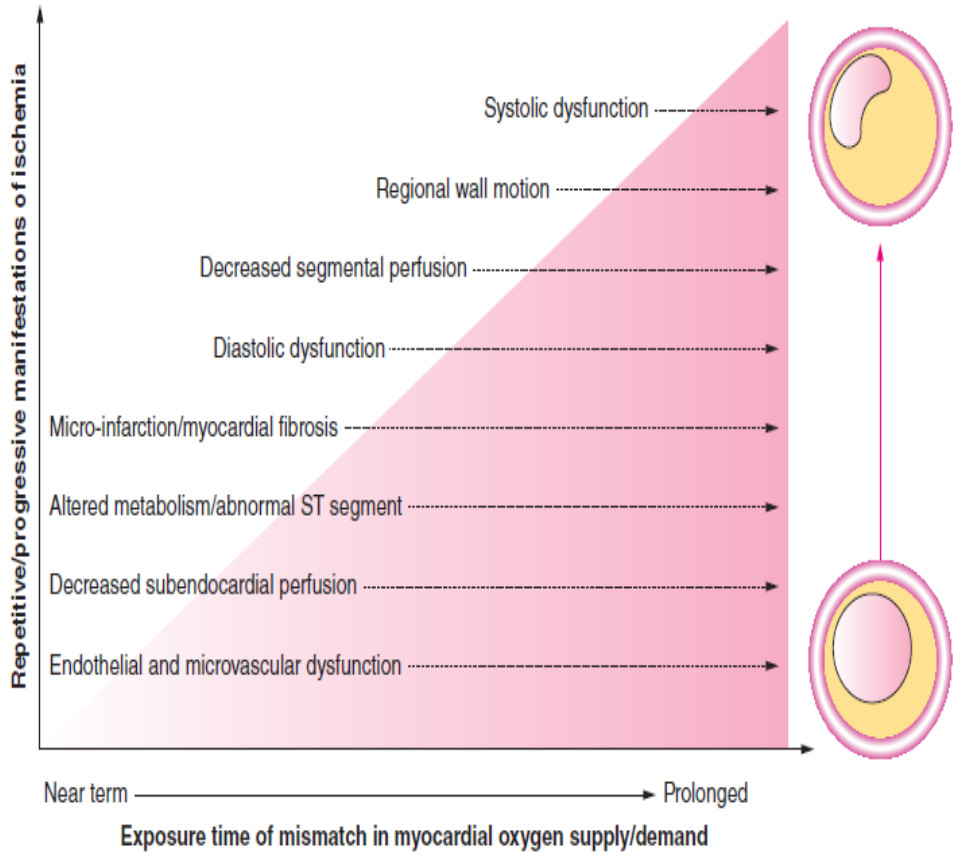
The major determinant of coronary resistance is found in R2 and R3 whereas R1 is trivial in the absence of significant flow-limiting atherosclerotic obstructions[62].

Atherosclerosis limits appropriate increases in perfusion when the demand for flow is augmented. It occurs during exertion or excitement by reducing the lumen of the coronary arteries . Myocardial perfusion in the basal state is reduced, when the luminal reduction is severe [62].

Myocardial ischemia also can occur if myocardial oxygen demands are markedly increased. It occurs when coronary blood flow may be limited, which occurs in aortic stenosis causing severe left ventricular hypertrophy. It can present with angina. It may be indistinguishable from that caused by coronary atherosclerosis largely owing to sub endocardial ischemia . Some conditions causes reduction in the oxygen carrying capacity of the blood like extremely severe anaemia or in the presence of carboxyhemoglobin, rarely causes myocardial ischemia by itself. It can also lower the threshold for ischemia in patients with moderate coronary obstruction[62].

Sometimes abnormal constriction or failure of normal dilation of the coronary resistance vessels also can cause ischemia. It can causes angina which is referred to as microvascular angina[62].

FIGURE 2 : CASCADE OF MECHANISMS AND MANIFESTATIONS OF ISCHEMIA[62].



EFFECT OF ISCHEMIA :

Episodes of inadequate perfusion caused by coronary atherosclerosis can lead to fall in myocardial tissue oxygen tension and may cause transient disturbances of the mechanical, biochemical, and electrical functions of the myocardium . Coronary atherosclerosis is a focal process. It causes non uniform ischemia.

During ischemia, regional disturbances of ventricular contractility can occur. It can cause segmental hypokinesia, akinesia, or, in severe cases, bulging or dyskinesia, which can lead to reduction of myocardial pump function[62].

The duration and severity of the imbalance between myocardial oxygen supply and demand is the major factor. It determine whether the damage is reversible (≤20 min for total occlusion in the absence of collaterals) or permanent with subsequent myocardial necrosis (>20 min)[62].

Most patients who die suddenly from IHD and the major cause is ischemia-induced ventricular tachyarrhythmias [62].

PROGNOSTIC INDICATORS :

The principal prognostic indicators in patients with IHD are

- Age
- The functional state of the left ventricle
- The location(s) and severity of coronary artery narrowing
- The severity or activity of myocardial ischemia.
- Angina pectoris of recent onset
- Unstable angina
- Early postmyocardial infarction angina
- Angina that is unresponsive or poorly responsive to medical therapy
- Angina accompanied by symptoms of congestive heart failure

indicate an increased risk for adverse coronary events[62].

PHYSICAL SIGNS INDICATING POOR PROGNOSIS :

- Signs of heart failure
- Episodes of pulmonary edema
- Transient third heart sounds
- Mitral regurgitation
- Echocardiographic or roentgenographic evidence of cardiac enlargement and reduced (<0.40) ejection fraction[62].

EVALUATION OF PATIENT WITH IHD :

- History of chest pain (typical angina), sweating, palpitation, reduced urine output, swelling of legs.
- Physical examination which includes signs of atherosclerosis, peripheral pulses, signs of failure, examination of cardiovascular system- should look for murmur, third/fourth heart sound.
- Laboratory investigations should be done – blood sugar, lipid profile, creatinine, hematocrit, thyroid function test based on the history.
- A 12 lead ECG may be normal at rest.So stress tesing is required.
- Coronary angiogram is indicated for :

- Patients with chronic stable angina pectoris who are severely symptomatic despite medical therapy and are considered for revascularization, i.e., a percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG).
- Patients with troublesome symptoms that present diagnostic difficulties in whom there is a need to confirm or rule out the diagnosis of IHD
- Patients with known or possible angina pectoris who have survived cardiac arrest
- Patients with angina or evidence of ischemia on noninvasive testing with clinical or laboratory evidence of ventricular dysfunction

- Patients judged to be at high risk of sustaining coronary events based on signs of severe ischemia on noninvasive testing, regardless of the presence or severity of symptoms[62].

MANAGEMENT :

- Patient should be explained about the condition and reassured.
- Aggravating factors such as left ventricular hypertrophy, aortic valve disease, HOCM should be treated.
- Adaptation of activity like avoiding the tasks that evoke angina should be done.
- Risk factors such as obesity, diabetes, hypertension, dyslipidemia should be treated with life style modifications and pharmacotherapy.
- Drug therapy : Antiplatelets, beta blockers, calcium channel blockers, nitrates
- Coronary revascularization : Percutaneous coronary intervention and coronary bypass grafting. In case of ST elevation MI, fibrinolytic therapy is indicated if the patient presents within 12 hours of symptom onset.

EPICARDIAL FAT (EPICARDIAL ADIPOSE TISSUE)

- Epicardial fat (EF) is the adipose tissue accumulated between the visceral pericardium and the myocardium[1].
- It do not have any fascia separating it from the myocardium and the epicardial vessels[1].
- It shares many of the pathophysiological properties of other visceral fat deposits[1] .
- It also potentially causes local inflammation and likely has direct effects on coronary atherosclerosis[1] .
- Echocardiography, computed tomography and magnetic resonance imaging have been used to evaluate EF[1] .

PHYSIOLOGICAL ROLES OF EPICARDIAL FAT :

- Local distribution and regulation of vascular flow by vasocrine. mechanisms[25] .
- Immune barrier, protecting the myocardium and coronary arteries. from inflammatory and pathogenic substances[26].
- Mechanical protection of the coronary arteries.
- Providing space for the arterial wall expansion in the early stages of atherosclerosis.
- Local source of fatty acids for the myocardium during of high-demand moments[27].
- Thermogenic effects related to brown adipose tissue[28].

BENEFICIAL EFFECTS OF PERICARDIAL ADIPOSE TISSUE AND EPICARDIAL ADIPOSE TISSUE :

The perivascular and epicardial fat are normally present in humans and other mammals should be emphasised[12]. However, the size of these fat depots is increased, commensurate with increases in visceral fat in obesity[12]. Therefore, this is hypertrophy of a normal anatomic structure and not "ectopic fat" per se [12].

EAT predominantly functions as perivascular adipose tissue (PVAT) for the coronary arteries. It is being concentrated in the acute marginal, atrio-ventricular, and interventricular sulci[10]. The walls of the ventricles are free of epicardial fat except the lateral wall of the right and the anterior wall of the left[10].

High rates of both lipogenesis and lipolysis is displayed by EAT and has been proposed to serve as local fat storage depot. It stores excess free fatty acids as triglyceride at times of excess. It releases them to the heart for substrate in times of metabolic stress[11]. PVAT surrounds large (aorta), medium-size (mesenteric), and small arteries (gluteal), in addition to surrounding the coronary arteries. It's function likely differs in each of these anatomic contexts[12].

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VASOPROTECTIVE FACTORS RELEASED FROM EAT[12] :

- Adiponectin
- Leptin
- Omentin-1
- Nitric oxide
- Palmic acid methyl ester
- PGI_2

PVAT expresses and secretes many putatively beneficial adipokines. Among them, adiponectin (ADIPOQ) appears to be the most prominent[11,13,14-17]. In lean humans, PVAT-derived ADIPOQ has vasodilatory properties on small arteries from gluteal fat[13]. This anticontractile function is lost in obesity. It is due to decreased PVAT ADIPOQ and increased TNF-alfa concentrations[13].

After gastric bypass and a mean reduction in BMI from 51.5 to 37.9 kg/m^2, the anticontractile effect of PVAT was restored, in conjunction with an increase in PVAT ADIPOQ concentrations[14]. This anticontractile effect was abrogated by preincubation with anti-AdipoR1 antibodies or removal of PVAT[13,14]. ADIPOQ also modulates endothelium-dependent vasodilation.

PVAT-derived ADIPOQ stimulates local endothelial nitric oxide synthetase (eNOS/NOS3) function via 2 mechanisms:

- stimulation of AKT-dependent phosphorylation
- increased - tetrahydrobiopterin (BH4) synthesis[17].

ADIPOQ also has potent anti-inflammatory effects in multiple cell types[18]. It suppresses adipocyte production of TNF-alfa and C-reactive protein[18]. ADIPOQ also suppresses activation of nuclear factor kappa-light-chain-enhancer of activated B cells in endothelial cells via

- cyclic AMP–protein kinase A
- AMP-regulated protein kinase pathways[19].

ADIPOQ suppresses IL-6, TNF-alfa, and scavenger receptor A expression in macrophages. It increases expression of the anti-inflammatory cytokine IL-10[18]. The specific anti-inflammatory effects of ADIPOQ vary based on the cellular context. They are also dependent on the concentration and molecular weight of the circulating hexamer (ie, low or high molecular weight)[19].

PATHOLOGICAL EFFECTS OF DYSREGULATED PERIVASCULAR ADIPOCYTES :

EAT is subject to the maladaptive adipocyte biology of obesity. Despite these putative beneficial effects, analogous to VAT, it is characterized by hypertrophy, failure to store triglyceride, increased lipolysis and inflammation. Here, the beneficial paracrine effects of EAT (ie, ADIPOQ release, fatty acid uptake) are abrogated. The causative role in local inflammation and CV pathophysiology may be assumed[12].

The mTORC2 suppress inflammatory cytokine expression. It also appears to suppress expression of inducible nitric oxide synthetase (iNOS/NOS2) by the adipocyte itself[20]. Downregulation of mTORC2 signaling causes induction of adipocyte iNOS. It leads to unregulated nitric oxide production and generation of ROS such as peroxynitrite (ONOO−). Thus the ROS directly cause vasoconstriction of vascular smooth muscle cells . This represents a provocative mechanism .Here the metabolic stress in adipocytes may simultaneously initiate inflammation and vasoconstriction[12].

In patients with advanced coronary artery disease (CAD), there is increased staining for CD11c+ cells in EAT .It is a marker of inflammatory (M1 or “classically activated”) macrophages[21]. In contrast, in patients without CAD, there is increased CD206+ staining. It is a marker of anti-inflammatory macrophage (M2 or “alternatively activated”) polarity[21]. The transition of

resident macrophages from a resting anti-inflammatory (M2) state to an activated (M1) state may be a manifestation of lipotoxicity[22].

In parallel to this inflammatory state in EAT, beneficial adipokine production is decreased in obesity[12].

PVAT from atherosclerotic abdominal aortas was found to secrete MCP-1 and IL-8. It is secreted in concentrations where it is equivalent to paired subcutaneous fat[23]. The functional significance of these factors was suggested by the ability of both subcutaneous fat and PVAT to stimulate leukocyte chemotaxis in transwell assays and the observation that CD68+ and CD3+ cells were present in PVAT[23]. EAT from patients with CAD was found to have higher mRNA. It also have protein levels of inflammatory cytokines (IL-1beta, IL-6, MCP-1, and TNF-alpha) than paired subcutaneous fat. Expression of these factors was associated with dense inflammatory infiltrates of macrophages, T cells, and mast cells in EAT[24].

BASIC MECHANISMS :

Some of the studies showed that tumor necrosis factor (TNF)-alpha levels were increased in the adipose tissue of obese humans and mice. They demonstrated infiltration of macrophages into the VAT of obese mice[2-3]

Chronic caloric excess in the face of reduced energy expenditure causes increased visceral fat mass. It occurs due to hypertrophy of individual adipocytes and hyperplasia of adipocyte precursors. Increased adipocyte size

results in the release of chemotactic factors such as monocyte chemoattractant protein-1 (MCP-1). It initiate the migration of monocytes into VAT and promote their differentiation into macrophages[5].

The trigger for the initiation of blood monocyte chemotaxis into VAT is multifactorial :

- Adipocyte apoptosis
- Increased lipolysis
- Local free fatty acids
- Reactive oxygen species
- Tissue hypoxia

play a role[6]. The differentiation of infiltrated monocytes into proinflammatory macrophages (M1 or "classically activated") results in the local production of cytokines such as interleukin (IL)-1beta, TNF-alpha, and IL-6[12].

TNF-alpha production by macrophages directly inhibits insulin signaling in adipocytes. It causes decreased glucose transport, decreased free fatty acid uptake and reesterfication, and increased lipolysis[7]. Based on these considerations, the resultant failure of VAT to store triglyceride could result in the ectopic accumulation of toxic fatty acids species (eg, diacylglycerol, ceramide). It gets accumulated in skeletal muscle, liver, pancreas, and

myocardium, which contribute to end-organ and ultimately systemic insulin resistance[7].

In particular, the proximity of inflamed VAT to the portal circulation allows released fatty acids and cytokines to directly affect the liver. It is thought to contribute to hepatic insulin resistance and hepatic steatosis[8].

Interestingly, some have suggested that epicardial adipose tissue (EAT) may play a similarly important role in myocardial steatosis. It may be due to its anatomic proximity and absence of a dividing fascial plane[9].

Finally, it should be emphasized that PVAT is an intimate part of the adventitia. It contains many different cell types (eg, adipocytes, endothelial cells, fibroblasts) with interrelated functions. Pathological conditions other than obesity such as hypertension, or balloon inflation during percutaneous intervention, may also initiate a response in PVAT[12].

MEASUREMENT AND IMAGING METHODS :

Echocardiographic allows adequate assessment of pericardial space in most clinical situations. It has been used to measure EF, mainly by Iacobellis et al[29], since 2003. Computed tomography (CT) and magnetic resonance imaging (MRI) have been traditionally used as adjuvants to echocardiography[1].

TWO-DIMENSIONAL ECHOCARDIOGRAPHY :

There is no consensus regarding its use in clinical practice. Some recommendations are suggested for EF measurement by echocardiography[30].

Epicardial fat thickness should be measured on the right ventricular free wall in at least two locations, from both parasternal longitudinal and transverse parasternal views, using the mean of three consecutive beats. These measurements show good correlation with the values found on MRI ($r = 0.91$, $p = 0.001$)[31].

EF is identified as a hypoechoic space anteriorly to the right ventricular wall and its thickness is measured between the epicardial surface and the parietal pericardium, identified by the sliding between these two layers. Epicardial fat should not be confused with pericardial fluid. On the other hand, pericardial fat is difficult to delimit by echocardiography. The critical issue with EF measurement is the inconsistency of measurement location due to spatial variations especially along the great vessels and the right ventricle. Anatomical landmark should always be used as a measurements, such as the position of interventricular septum and the aortic annulus[32].

Even though some of these studies have suggested higher cut-offs, measurements, > 5 mm should represent a relevant cut-off to define increased EF, especially in low-risk populations.

DETERMINANTS OF EPICARDIAL FAT

There is a broad individual variation in the amount and distribution of EF, attributable to their clinical and demographic characteristics[1].

OBESITY :

Reduction in body weight (mean reduction of 40 ± 14 kg) in patients undergoing bariatric surgery decreased the EF thickness from 5.3 ± 2.4 mm to 4.0 ± 1.6 mm[33].

AGE :

Epicardial fat seems to increase with age[34,35,39]. It is 22% thicker in individuals older than 65 years[36]. During the aging process, there is a decrease in lean body mass and increase in fat mass. There is fat tissue redistribution to the trunk and viscera[37]. These changes seem to occur at a different rate and intensity between men and women. But a greater redistribution seen in older women[38].

GENDER :

There is no consensus in the literature on the impact of gender on the amount of epicardial fat. Based on the data from the Framingham cohort, Rosito et al[40] suggest that EF is more associated with risk factors in women than in men.

ETHNICITY :

Ethnicity may also contribute to the amount of EF. In general, individuals with black skin color have less central obesity than whites. But they are more insulin-resistant[41]. It suggest that in those with black skin color, the adiposity has a more diabetogenic than atherogenic nature, by mechanisms not yet clearly understood[42].

CLINICAL ASSOCIATIONS

METABOLIC SYNDROME AND DIABETES MELLITUS :

Most studies [40,43-49]described a higher amount of EF in individuals with metabolic syndrome (MS). It has across different clinical characteristics and prevalence of MS.

Inflammation[43,50-52], derangements in insulin sensitivity31,65 and arterial hypertension[48,54,57], which characterize MS, have been associated with EF. In general, there is a moderate association between EF and MS. Most of these effects can be explained by obesity.

Epicardial fat is also moderately associated with glycemic levels[55] and with the prevalence of DM[56].

CORONARY ARTERY DISEASE :

A direct association between the amount of EF and the presence/severity of coronary artery disease (CAD) is identified in observational studies in patients undergoing coronary angiography [1].

OTHER ASSOCIATIONS :

It is speculated that the increase in EF and fatty infiltration in the myocardium may cause other deleterious effects, such as

- Interfering with diastolic relaxation
- Affecting the cardiac conduction system
- Predisposing to AF[58,59].

EF is inversely associated with ejection fraction and left ventricular mass[60,61].

Thus various studies says that

The epicardial fat is a visceral fat deposit. It partially shares its systemic metabolic and inflammatory effects. Also, there is a rationale for the local atherosclerotic effect of EF on the coronary artery walls. EF is consistently associated with metabolic syndrome and coronary artery disease. But the magnitude of these associations is probably lower than previously expected[1].

METHODOLOGY

Place of study : Department of Internal Medicine,

Thanjavur Medical College and Hospital.

Collaborating Department : Department of Cardiology,

Thanjavur Medical College and Hospital.

Duration of the study : March 2017 – August 2017

Type of study : Case control study.

STUDY POPULATION :

- A Study group of 53 patients admitted with acute coronary syndrome at Thanjavur Medical College were included.
- A control group of 53 peoples who are not a known case of CAD (Coronary Artery Disease) were included.
- Epicardial fat pad thickness was measured using transthoracic echocardiogram for both the study group and the control group.
- Consent of the patients in study group and control group was taken.

INCLUSION CRITERIA :

1. Patients presenting with acute coronary syndrome.
2. Age above 20 years.
3. Both males and females.

EXCLUSION CRITERIA :

1. Patients with chronic kidney disease.
2. Known case of hypothyroidism.
3. Patient with decompensated liver disease.
4. Refusal to participate.

The patients who were included in study group and those in the control group were subjected to the following questionnaire :

- Detailed history of presenting symptoms – chest pain, palpitation, sweating.
- Past history of diabetes mellitus, hypertension, coronary artery disease and family history of coronary artery disease.
- Personal history regarding smoking, alcohol, diet, sedentary life style.

CLINICAL EXAMINATION :

All patients in the study group and those in the control group are meticulously examined for

- Blood pressure, pulse rate, jugular venous pulse (JVP), peripheral pulses
- A thorough examination of cardiovascular system , respiratory system, gastrointestinal system and central nervous system was done .

ANTHROPOMETRY :

Both the groups were subjected for the following measurements.

a. Height
b. Weight
c. Body Mass Index (BMI)
d. Waist / Hip Ratio

LABORATORY INVESTIGATIONS :

Both the groups were subjected to the following investigations.

a. Complete Blood Count
b. Fasting Blood Sugar
c. Fasting Lipid profile

ELECTROCARDIOGRAM :

A standard 12 lead resting electrocardiogram was taken for both the study group and the control group.

TRANSTHORACIC ECHOCARDIOGRAPHY :

Each subject underwent detailed transthoracic two-dimensional echocardiography with the subjects in left lateral decubitus position in the Department of Cardiology, Thanjavur Medical College Hospital, Thanjavur.

Epicardial fat pad thickness which is the echo free space between the outer layer of myocardial wall and the visceral layer of the pericardium was measured on the free wall of the right ventricle from both parasternal long and short axis views at mid ventricle during end diastole.

The maximum values at each site were measured and the average value was consider. P value less than 0.05 was considered as significant.

REFERENCE VALUES USED IN THE STUDY :

BMI (WHO criteria for Asian population)

Body Mass Index = Weight (Kg) / Height (meters)^2

Values	< 18.5 Kg/m^2	- Underweight
	18.5– 22.9 Kg/m^2	- Normal weight
	23 – 29.9 Kg/m^2	- Overweight
	> 30 Kg/m^2	- Obesity

WAIST HIP RATIO :

Waist circumference >94 cm (M); > 80 cm (W) - Increased

Waist circumference >102 cm (M); > 88 cm (W) - Substantially increased

Waist–hip ratio ≥ 0.90 cm (M); ≥ 0.85 cm (W) - Substantially increased

M- men; W- women

DATA MANAGEMENT AND ANALYSIS :

Data was entered into Microsoft Excel. Statistical analysis was done using software Graph Pad Prism Version 5. Data were expressed as mean with standard deviation. Categorical values were reported using number and percentage. Probability value (p valve) less than 0.05 was considered as statistically significant.

RESULTS

Table 1: Comparison of age in years between cases and controls in the study population

S. No	Age (in years)	Control group (n=53)		Case group (n=53)		P Value	Statistical test
		Mean	SD	Mean	SD		
1	Overall	33.28	9.39	54.6	12.06	<0.0001*	Unpaired 't' test
2	Male	31.9	9.24	53.31	12.28	<0.0001*	Unpaired 't' test
3	Female	34.8	9.5	62.13	7.51	<0.0001*	Unpaired 't' test

In this study the case group are of older age group compared to control group. Both males and females in case group are of older age group compared to the control group.

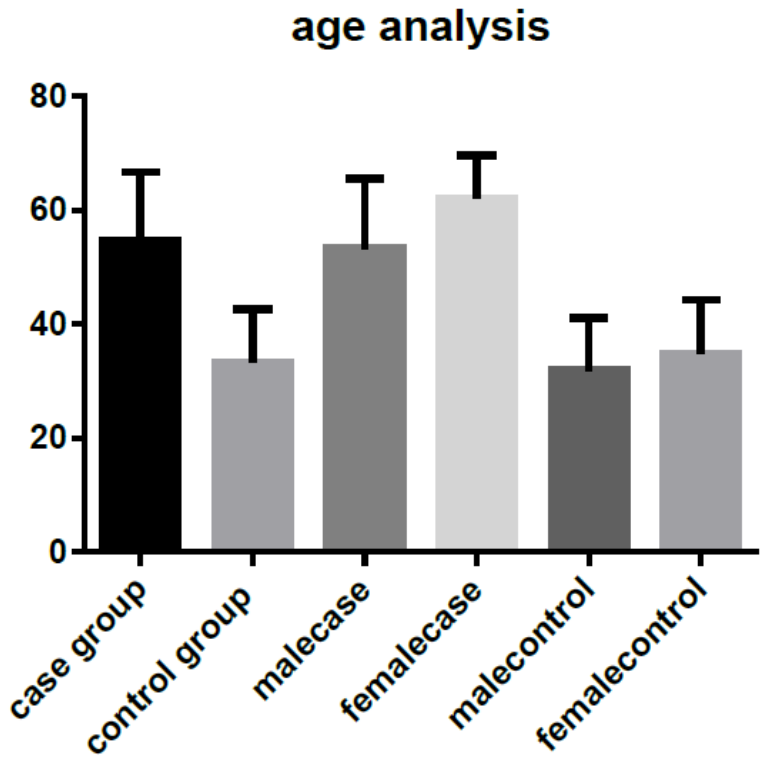


FIGURE 3: AGE DISTRIBUTION VS CASES/CONTROLS, MALE/FEMALE, MALE CONTROL/FEMALE CONTROL

Table 2: Comparison of gender proportion between the groups in the study population

S. No	Parameter	Control group (n=53)				Case group (n=53)				P Value	Statistical test
		Male		Female		Male		Female			
		n	%	n	%	n	%	n	%		
1	Gender proportion	28	52.8	25	47.2	45	84.9	8	15.1	0.0007*	Fisher's exact test

In the study, 28 were males and 25 were females in the case group. In the control group 45 were males and 8 were females.

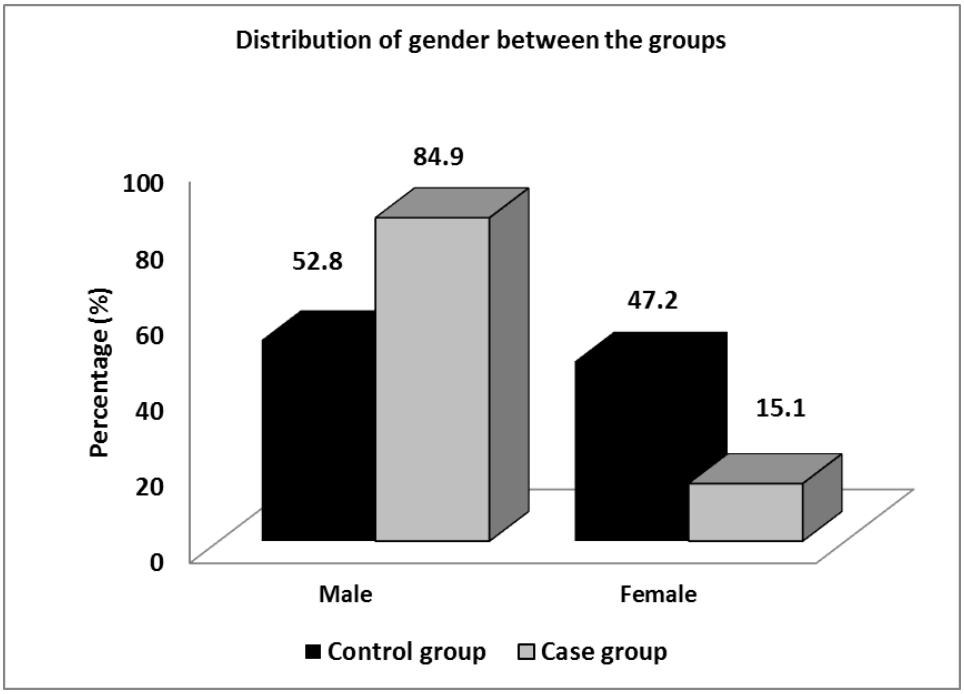


FIGURE 4: DISTRIBUTION OF GENDER BETWEEN THE GROUPS IN THE STUDY POPULATION

Table 3: Comparison of BMI between the control and case groups in the study population

S. No	BMI (Kg/m^2)	Control group		Case group		P Value	Statistical test
		Mean	SD	Mean	SD		
1	Overall (n=53/group)	21.9	2.04	24.1	2.18	<0.0001**	Unpaired 't' test
2	Normal weight (<22.9) (n=32 in control & n= 16 in case)	20.5	1.05	21.7	1.04	0.0009*	Unpaired 't' test
3	Overweight (≥22.9) (n=21 in control & n= 37 in case)	24.1	1.01	25.1	1.64	0.012*	Unpaired 't' test

In the study, body mass index for case group was higher when compared to the control group. On comparing both the normal weight and overweight individuals in case and control group, BMI is higher in case group.

Table 4: Frequency distribution of BMI types in the groups of the study

S. No	BMI (Kg/m^2)	Control group (n=53)		Case group (n=53)		P Value	Statistical test
		n	%	N	%		
1	Normal weight (<22.9)	32	60.3	16	30.1	0.0032*	Fisher's exact test
2	Overweight (≥22.9)	21	39.7	37	69.9		

Among the case group 16 were normal weight and 37 were overweight whereas in control group 32 were normal weight and 21 were overweight.

Table 5: Comparison of waist/hip ratio between the control and case groups in the study population

S. No	Waist hip Ratio	Control group		Case group		P Value	Statistical test
		Mean	SD	Mean	SD		
1	Overall (n=53/group)	0.92	0.07	0.96	0.08	0.0062*	Unpaired 't' test
2	Normal W/H ratio (n= 12 in control and n=8 in cases)	0.84	0.02	0.84	0.03	0.87(NS)	Unpaired 't' test
3	High W/H ratio (n= 41 in control and n =45 in cases)	0.94	0.06	0.99	0.07	0.0065*	Unpaired 't' test

In the study the case groups were having increased waist hip ratio compared to the case group were more than the control group.

Table 6: Frequency distribution of types of Waist hip ratio in the groups of the study population

S. No	Parameter	Control group (n=53)		Case group (n=53)		P Value	Statistical test
		n	%	N	%		
1	Normal Waist hip ratio	12	22.6	8	15.1	0.45 (NS)	Fisher's Exact test
2	High Waist Hip ratio	41	77.4	45	84.9		

Among the case group 12 were having normal waist hip ratio and 41 were having high waist hip ratio. Among the control group 8 were having normal waist hip ratio and 45 were having increased waist hip ratio.

Table 7: Comparison of fasting blood sugar levels between the groups with respect to weight (based on BMI and Waist Hip ratio).

S. No	Condition	Control group FBS (mg/dl)			Case group FBS (mg/dl)			P Value	Statistical test
		n	Mean	SD	n	Mean	SD		
1	Overall	53	102.1	27	53	148.2	82.7	0.02*	Mann Whitney U test
2	Normal weight (BMI <22.9 and Normal waist hip ratio)	12	94.3	31.5	5	145.8	104.9	0.22 (NS)	Mann Whitney U test
3	Overweight (BMI ≥22.9 or elevated waist hip ratio or both)	41	104	25.5	48	148.4	81.7	0.001**	Mann Whitney U test

In this study, fasting blood sugar was higher in case group compared to the control group. Among the study group and the control group those who are overweight, the fasting blood sugar was higher in the study group.

Table 8: Comparison of total cholesterol level between the groups with respect to weight (based on BMI and Waist Hip ratio).

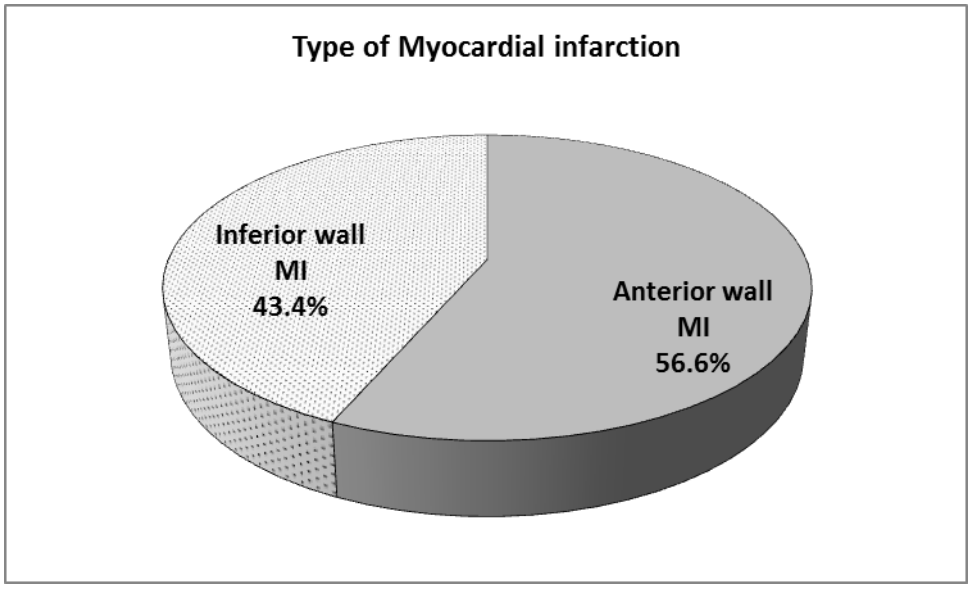
S. No	Condition	Control group Total cholesterol (mg/dl)			Case group total cholesterol (mg/dl)			P Value	Statistical test
		n	Mean	SD	n	Mean	SD		
1	Overall	53	127.9	18.3	53	183.2	43.7	<0.0001 *	Unpaired 't' test
2	Normal weight (BMI <22.9 and Normal waist hip ratio)	12	117.9	15.5	5	224.2	57	<0.0001 *	Unpaired 't' test
3	Overweight (BMI ≥22.9 or elevated waist hip ratio or both)	41	130.8	18.2	48	178.9	40.5	<0.0001 *	Unpaired 't' test

In the study total cholesterol level was high in case group compared to the control group. Among the case group both normal weight and overweight individuals were having high total cholesterol level than the control group.

Table 9: Frequency distribution of types of myocardial infarction in the case groups (n=53)

S. No	Type of myocardial infarction	Number (n)	Frequency (%)
1	Anterior wall MI	30	56.6
2	Inferior wall MI	23	43.4

FIGURE 5: FREQUENCY DISTRIBUTION OF TYPE OF MYOCARDIAL INFARCTION IN THE CASE GROUP



Among the case group, 30 were admitted with anterior wall myocardial infarction and 23 were admitted with inferior wall myocardial infarction.

Table 10: Comparison of epicardial fat pad thickness between the groups with respect to weight (based on BMI and Waist Hip ratio).

S. No	Condition	Control group epicardial pad fat thickness (mm)			Case group epicardial pad fat thickness (mm)			P Value	Statistical test
		n	Mean	SD	n	Mean	SD		
1	Overall	53	3.3	0.86	53	9.3	2.05	<0.0001**	Unpaired 't' test
2	Normal weight (BMI <22.9 and Normal waist hip ratio)	12	2.58	0.9	5	7.8	2.28	0.0003*	Mann Whitney U test
3	Overweight (BMI ≥22.9 or elevated waist hip ratio or both)	41	3.51	0.74	48	9.47	1.99	<0.0001**	Unpaired 't' test

The epicardial fat pad thickness in the case group was significantly higher in case group compared to the control group. Among the case group both normal weight and overweight individuals are having significantly higher epicardial fat pad thickness compared to control group.

Table 11. Cutoff values for the epicardial thickness in mm in various groups of patient to determine the development of MI.

S. No	Condition	Epicardial fat pad thickness in mm			
		Cut off value	Sensitivity	Specificity	Likelihood ratio
1	Overall	>5.5 mm	98.11%	92.45%	13
2	Normal weight (BMI <22.9 and Normal waist hip ratio)	>3.5 mm	100%	91.67%	12
3	Overweight (BMI ≥22.9 or elevated waist hip ratio or both)	>4.5 mm	100%	92.6%	13.6

By transthoracic echocardiography, if the epicardial fat pad thickness is more than 5.5 mm, the likelihood ratio for developing myocardial infarction is 13.

Table 12: Association of smoking and diabetes with the incidence of MI in the study population

S. No	Condition		Cases group (n=53)		Control group (n=53)		P Value	Statistical test
			n	%	n	%		
1	Smoking	Yes	9	16.9	6	11.3	0.578 (NS)	Chi-square test
		No	44	83.1	47	88.7		
2	Diabetes	Yes	14	26.4	6	11.3	0.08 (NS)	Chi-square test
		No	39	73.6	47	88.7		

In this study , smoking and known diabetes mellitus were not associated with the development of myocardial infarction.

DISCUSSION

- Out of 53 patients in the case group, the number of patients in the age group of 20-40 years were 9 (16.98%) , the number of patients in the age group of 40-60 years were 25 (47.16%) and the number of patients above 60 years were 35.84%.
- Out of 53 patients in the control group , the number of patients in the age group of 20-40 years were 42 (79.24%) , the number of patients in the age group of 40-60 years were 11 (20.75%) and the number of patients above 60 years was nil.
- Majority of the cases were in the age group of 40-60 years.
- The incidence of atherosclerosis and metabolic syndrome increases with age.
- 28 (52.8%) were males in the case group and 25 (47.2%) were females.
- Body mass index (BMI) was higher in the case group. 69.9 % (37 out of 53) of the patients in the case group fell in the category of overweight (> 22.9)
- There is positive association between central obesity and atherosclerosis and coronary artery disease.
- In normal weight patients in case group, BMI was comparatively higher than control group.

- 45 patients (77.4 %) out of 53 in the case group had high waist hip ratio.
- Waist hip ratio which is the marker of central obesity is associated with increased incidence of atherosclerosis and myocardial infarction.
- 25 (47.16%) patients out of 53 in case group were having high fasting blood sugar level.
- But only 14 (26.41%) out of 53 in case group were already known case of diabetes mellitus.
- So, 11 (20.75%) out of 53 patients in the case group were not aware of their glycemic status and was found to be diabetic during hospital admission.
- 15 (28.3%) out of 53 patients in the case group had high total cholesterol level.
- On comparing overweight cases and controls and normal weight cases and controls the total cholesterol level in case group was more than the control group.
- Out of 53 patients in the case group, 30 (56.6 %) were admitted with anterior wall MI and 23 (43.4%) were admitted with inferior wall MI.
- Smoking was not associated with incidence of MI in this study.
- Epicardial fat pad thickness measured by transthoracic echocardiography shows that it was significantly higher in case group compared to the control group.

- From the analysis it was found that the cut off value for the epicardial thickness is > 5.5 mm which had 98.11% sensitivity and 92.45% specificity when detected by transthoracic echocardiography and the likelihood ratio is 13.

With the above data, analysis was done.

- Older age group was found to be statistically significant (p value - < 0.0001)
- BMI was found to be statistically significant (p value - < 0.0001)
- Waist hip ratio was found to be statistically significant (p valve – 0.0062)
- Smoking was not found to be statistically significant.
- Fasting blood glucose level was found to be statistically significant (p valve – 0.02)
- Total cholesterol level was found to be statistically significant (p value - <0.0001)
- Epicardial fat pad thickness was found to be statistically significant. (p value - < 0.0001)
- The sensitivity of epicardial fat pad thickness measurement by transthoracic echocardiography was 98.11% and was 92.45%

SUMMARY

- Epicardial fat pad thickness is the marker of overall content of visceral adipose tissue in the body.
- The presence of increased visceral adipose tissue is strongly associated with metabolic syndrome.
- The presence of EAT (Epicardial adipose tissue) , measured by transthoracic echocardiography showed good correlation with waist circumference, BMI, fasting glucose level and total cholesterol level.
- Thus EAT is emerging as an important and good marker for metabolic syndrome.
- Thus those with increased EAT thickness , other screening test for metabolic syndrome should be done.
- Even in the clinically nonobese patients , the presence of visceral obesity has the increased cardiovascular risk and they are at the risk of developing acute coronary syndrome in the future and this risk can be predicted by measuring EAT thickness by transthoracic echocardiography.
- For these people life style modification should be encouraged and if needed pharmacological treatment should be started.

- In one of the previous study, association of increased epicardial fat pad thickness with left atrial enlargement, lower ejection fraction, increased left ventricular mass and abnormal diastolic function was described[61].
- In this study , since epicardial adipose tissue has positive correlation with metabolic syndrome and myocardial infarction. EAT screening can be included under routine metabolic screening.
- In a recent study, the median values of end systolic measurement of EAT >9.5 mm for men and >7.5 mm for women was associated with the metabolic syndrome[70].
- A recent study showed that EAT thickness of greater than 12.4 mm correlated with the presence of at least two markers of metabolic syndrome including hypertension, dyslipidemia, and hyperglycemia[71].
- In this study, EAT thickness of >5.5 mm is the cut off value and the sensitivity by measuring with transthoracic echocardiography is 98.11% and the specificity is 92.45% .
- Thus by measuring EAT thickness by transthoracic echocardiography, future cardiovascular risk can be predicted.

CONCLUSION

- EAT thickness has a positive correlation with metabolic syndrome and cardiovascular risk and is a more sensitive assessment of body fat distribution.
- EAT can also be measured by various imaging modalities like CT and MRI, but they are expensive.
- Transthoracic echocardiography provided a relatively inexpensive means to measure and quantify EAT, which is an important component of VAT.
- It does not require any specific training.
- It is not a time consuming and only adds minimally to the time required for regular echocardiographic procedure.
- By adding this simple and inexpensive measure along with waist-hip ratio, BMI and other routine tests for metabolic syndrome helps predict cardiovascular risk.

LIMITATIONS OF THE STUDY

- Small study population
- Small study period of 6 months
- Study population includes population predominantly from Thanjavur and surrounding areas and hence cannot be generalised to the entire population.
- EAT thickness cannot be measured accurately by transthoracic echocardiogram
- Inter-observer variations can occur.
- More accurate markers of glycemic status like HbA1c was not readily available for analysis and hence not included.

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ANNEXURE A1

MASTER CHART

KEY TO MASTER CHART

1. AGE – IN YEARS
2. GENDER – M – MALE, F – FEMALE
3. BMI – IN KG/M^2
4. W/H RATIO – WAIST/HIP RATIO
5. FBS – FASTING BLOOD SUGAR – IN MG/DL
6. TOT CHO – TOTAL CHOLESTEROL – IN MG/DL
7. MI –MYOCARDIAL INFARCTION – AWMI – ANTERIOR WALL MI, IWMI – INFERIOR WALL MI
8. EPI FAT – EPICARDIAL FAT THICKNESS – IN MM
9. DIABETES – YES OR NO
10. SMO/ALC – SMOKER/ALCOHOLIC – YES OR NO

CASE GROUP

NAME	AGE	GENDER	BMI	W/H RATIO	FBS	TOT.CHO	MI	EPI FAT	DIABETES	SMO/ALC
Ilayaraja	25	M	23.38	0.98	76	150	AWMI	12 mm	NO	NO
Fahima mary	56	F	22.83	1.03	280	156	AWMI	10 mm	YES	NO
Vijayakumar	38	M	22.75	1.02	124	183	AWMI	12 mm	NO	NO
Marimuthu	45	M	23.18	0.96	83	126	IWMI	8 mm	NO	NO
Lakshmanan	35	M	25.39	1.05	85	187	AWMI	10 mm	NO	NO
Vadivel	53	M	19.6	0.92	74	175	AWMI	8 mm	NO	NO
Kaliaperumal	64	M	24.2	0.96	342	150	AWMI	7 mm	YES	NO
Navaneethan	65	M	29.38	1.08	181	250	AWMI	12 mm	YES	YES
Arulanandham	67	M	29.25	1.1	320	180	AWMI	6 mm	YES	NO
Pandi	37	M	24.38	0.9	89	125	IWMI	8 mm	NO	NO
Shajathah	60	M	25.39	1.03	91	178	AWMI	10 mm	NO	YES
Alamelu	55	F	24.97	0.96	150	184	AWMI	8 mm	NO	NO
Dhanabakiyam	70	F	24.97	1.1	79	158	IWMI	7 mm	NO	NO
Yesuraja	50	M	24.21	0.92	155	175	IWMI	9 mm	NO	NO
Murugesan	68	M	23.26	0.81	69	125	IWMI	7 mm	NO	NO
Nadarajan	62	M	20.34	0.87	91	285	IWMI	8 mm	NO	NO
Chelladurai	68	M	21.56	0.91	217	120	IWMI	6 mm	YES	NO
Sathyaraj	28	M	21.42	0.82	92	151	AWMI	9 mm	NO	YES
Gurumoorthi	40	M	22.36	0.84	331	278	IWMI	8 mm	YES	NO
Sagar	50	M	28.56	1.04	96	197	AWMI	12 mm	NO	YES
Rani	65	F	24.72	0.91	84	238	AWMI	12 mm	NO	NO
Tamilvannan	61	M	22.45	0.93	104	270	AWMI	12 mm	NO	YES
Sadasivam	67	M	23.78	0.89	92	224	IWMI	10 mm	NO	NO
Ganesan	70	M	25.61	0.93	93	216	AWMI	8 mm	NO	NO
Raja	44	M	24.43	0.84	107	178	IWMI	6 mm	NO	NO
Tamilselvan	55	M	19.54	0.81	86	193	AWMI	4 mm	NO	NO
Sivaraman	53	M	24.27	0.91	184	145	AWMI	10 mm	NO	NO
Chelladurai	56	M	24.34	0.94	217	120	IWMI	6 mm	YES	NO
Sekar	50	M	21.67	0.91	317	196	AWMI	12 mm	YES	YES
Vijaya	50	F	24.49	1.06	153	206	AWMI	8 mm	NO	NO
Shafath	68	M	22.05	0.97	285	145	AWMI	8 mm	YES	NO
Marthaiyan	50	M	23.18	0.97	183	184	AWMI	10 mm	YES	NO
Krishnammal	67	F	26.6	1.12	285	193	IWMI	10 mm	YES	NO
Balu	58	M	23.67	0.97	145	230	AWMI	8 mm	NO	NO
Velu	74	M	24.37	1.03	171	196	IWMI	10 mm	NO	NO
Antonyraj	45	M	22.64	0.87	129	214	AWMI	10 mm	NO	YES
Mariyadass	55	M	25.73	1.08	169	253	IWMI	12 mm	NO	NO
Murugesan	40	M	25.53	1.12	74	205	AWMI	12 mm	NO	NO
Nagaboosanam	64	M	24.43	0.93	132	174	AWMI	8 mm	NO	NO
Mariyajoseph	53	M	22.26	0.91	103	149	AWMI	10 mm	NO	NO
Karupaiya	60	M	22.35	0.94	84	177	IWMI	9 mm	NO	NO
Rajkumar	35	M	26.74	1.07	243	189	IWMI	9 mm	YES	NO
Sathyamoorthy	37	M	24.57	0.91	82	111	IWMI	12 mm	NO	NO
Sundaramoorthy	60	M	24.09	1.03	90	160	AWMI	10 mm	NO	NO
Kalaiselvan	60	M	24.16	0.98	89	192	AWMI	12 mm	NO	YES
Govindharaj	55	M	27.34	1.16	60	215	IWMI	9 mm	NO	NO
Kalavathy	64	F	23.67	0.94	58	208	IWMI	10 mm	NO	NO
Mohammed Rafik	35	M	26.87	1.09	100	270	IWMI	12 mm	NO	NO
Mohan	53	M	22.06	0.92	138	127	IWMI	8 mm	NO	NO
Palaniyammal	70	F	24.08	0.98	286	194	IWMI	12 mm	YES	NO
Anbalagan	53	M	21.48	0.92	73	122	IWMI	8 mm	NO	NO
Ulaganadhan	65	M	26.7	0.9	282	140	AWMI	12 mm	YES	YES
Srinivasan	68	M	27.34	1.11	130	142	AWMI	8 mm	NO	NO

CONTROL GROUP

NAME	AGE	GENDER	BMI	W/H RATIO	FBS	TOL.CHO	EPI FAT	DIABETES	SMO/ALC
Rathinam	30	M	21.29	0.91	93	154	3 mm	NO	YES
Saminayagam	58	M	23.56	0.94	77	142	4 mm	NO	NO
Magilammal	46	F	24.89	1.02	120	135	4 mm	NO	NO
Abiya	28	F	19.76	0.83	110	121	2 mm	NO	NO
Ambika	22	F	19.53	0.81	80	124	2 mm	NO	NO
Kalaiselvi	27	F	21.06	0.85	84	133	3 mm	NO	NO
Rajalakshmi	29	F	20.07	0.91	79	114	3 mm	NO	NO
Anushya	21	F	19.06	0.87	94	126	2 mm	NO	NO
Savithri	55	F	22.12	0.92	116	146	4 mm	NO	NO
Selvapriya	24	F	21.07	0.83	62	112	3 mm	NO	NO
Saroja	49	F	24.28	1.03	133	147	4 mm	NO	NO
Dinesh	28	M	20.21	0.94	80	129	3 mm	NO	YES
Anand	23	M	19.04	0.84	164	135	3 mm	YES	NO
Fathima	48	F	24.37	0.97	112	154	4 mm	NO	NO
Geetha	27	F	20.97	0.83	96	131	3 mm	NO	NO
Jothilakshmi	32	F	24.06	1.11	117	143	4 mm	NO	NO
Vellaiyammal	51	F	22.07	0.86	156	148	5 mm	YES	NO
Abirami	25	F	19.05	0.85	83	106	2 mm	NO	NO
Usha	32	F	22.08	0.91	52	112	3 mm	NO	NO
Periyasamy	37	M	24.31	0.95	134	157	3 mm	YES	YES
Dhanush	24	M	20.03	0.91	114	136	3 mm	NO	NO
Sarathkumar	25	M	21.04	0.93	58	142	3 mm	NO	NO
Rajasekaran	35	M	23.48	0.96	78	132	4 mm	NO	YES
Appar	40	M	23.31	0.95	104	164	4 mm	NO	NO
Aravind	25	M	19.21	0.89	74	111	2 mm	NO	NO
Vengatesh	25	M	20.31	0.87	61	114	2 mm	NO	NO
Subramaniyan	34	M	25.54	1.04	68	148	4 mm	NO	NO
Riyas	27	M	19.42	0.92	84	116	2 mm	NO	NO
Ilayabharathi	29	M	20.03	0.93	112	132	3 mm	NO	NO
Ilamparidhi	22	M	21.02	0.87	74	103	2 mm	NO	NO
Vinoth	23	M	20.06	0.92	63	115	3 mm	NO	NO
Vincent	25	M	21.08	0.93	87	122	3 mm	NO	NO
Senthil kumar	29	M	24.19	0.97	126	154	4 mm	NO	YES
Rajesh kumar	31	M	27.12	1.06	96	114	3 mm	NO	NO
Gokulanadhar	39	M	23.04	0.97	133	157	5 mm	NO	NO
Saran kumar	28	M	19.14	0.87	89	103	2 mm	NO	NO
Selva kumar	34	M	25.07	1.11	121	140	4 mm	NO	NO
Paulraj	50	M	24.43	0.97	156	164	5 mm	YES	NO
Balaguru	38	M	24.04	0.91	142	114	4 mm	YES	NO
Naveena	27	F	21.03	0.83	82	103	2 mm	NO	NO
Revathi	32	F	22.09	0.87	112	130	3 mm	NO	NO
Saritha	36	F	23.07	0.94	104	112	3 mm	NO	NO
Susila	39	F	24.03	1.04	112	135	4 mm	NO	NO
Seetha	31	F	23.05	0.92	123	117	4 mm	NO	NO
Muthulakshm	42	F	23.03	0.87	138	109	4 mm	NO	NO
Bhuvana	35	F	21.75	0.86	113	108	4 mm	NO	NO
Amardeen	29	M	20.21	0.9	88	107	3 mm	NO	NO
Logesh	28	M	21.02	0.91	79	101	3 mm	NO	NO
Akash	25	M	19.09	0.81	96	105	3 mm	NO	NO
Rajagopal	53	M	22.04	0.87	144	153	5 mm	YES	YES
Kanimozhi	33	F	22.06	0.92	112	104	4 mm	NO	NO
Pushpa	37	F	25.03	1.12	121	133	4 mm	NO	NO
Sagunthala	42	F	23.04	0.97	105	112	3 mm	NO	NO

ANNEXURE A2

PROFORMA

CORRELATION BETWEEN EPICARDIAL FAT PAD THICKNESS AND ACUTE CORONARY SYNDROME

DEMOGRAPHIC DATA:

NAME :

AGE: GENDER:

ADDRESS:

PHONE NO:

HISTORY AND PHYSICAL EXAMINATION:

	YES	NO
CHEST PAIN :		
DYSPNOEA:		
PALPITATION:		
DIABETES MELLITUS:		
HYPERTENSION:		
H/O ACS :		
IF YES,DETAILS :		
DYSLIPIDEMIA:		
FAMILY H/O CVD:		
SEDENTARY LIFE STYLE:		
OBESITY:		

SMOKING/TOBACCO USE:

BP - PR -

JVP - CVS -

ANTHROPOMETRY:

HEIGHT: WEIGHT:

BMI:

WAIST/HIP RATIO:

INVESTIGATIONS:

CBC:

BLOOD SUGAR:

LIPID PROFILE:

ECG:

ECHO INCLUDING EPICARDIAL FAT:

ANNEXURE A3

CONSENT FORM

I _____ hereby give consent to participate in the study conducted by **DR P.K.DEEPTHI ,** Post graduate in the Department of General Medicine ,Thanjavur Medical College & Hospital, Thanjavur – 613004 and to use my personal clinical data and result of investigation for the purpose of analysis and to study the nature of disease. I also give consent for further investigations

Place :

Date : Signature of participant